DATE: October 15, 2001

FROM: Daniel Kearns, HFM-675

TO: Serono STN 103780/0 file (G. Johnson, HFM-541; original to S. Giuliani, HFM-588)

THROUGH: Carol Rehkopf, Acting Branch 1 Chief, HFM-675

SUBJECT: Review of Serono May 16, 2001 amendment for Rebif® (interferon beta-1a) – changes to the labeling and CMC sections

CONCLUSION: The submission appears to have submitted all information for an amendment for changes to the CMC section of an application in accord with CBER's "Guidance for Industry: For the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use." The data and information submitted appears to support the conclusion that the changes are reasonable and that the product is comparable to the product made that is the subject of the original application.

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BACKGROUND

This is an amendment to Serono's BLA 98-0261 (now BL 103780/0) which (i.e., the BLA) was initially submitted on February 28, 1998. The labeling in the May 16, 2001 submission was withdrawn and later resubmitted. In a meeting held on July 19, 2001, CBER acknowledged that the May 16, 2001 response was a complete class 2 response, with a final action milestone of November 17, 2001. However, as Serono intends to submit additional amendments, CBER proposed to Serono that the May 16, 2001 response not be considered a complete response, to accommodate the PDUFA milestones – Serono concurred with this course of action. Serono has stated, per the May 16, 2001 meeting agreement, that their September 4, 2001 amendment is their (Serrano's) complete response. The September 4, 2001 amendment provides additional clinical data in response to CBER's January 2, 2001 letter. Also, noted in the September 4, 2001 response is that all the manufacturing changes in this BL amendment have been reported to the applicable IND (XXXXXXXXXX). CBER also stated that CBER's intent was to review the CMC data submitted in the May 16, 2001 prior to the action date for that submission (i.e., November 17, 2001).

REFERENCES

"Guidance for Industry: Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products" CBER, July 1997.
"Guidance for Industry: For the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use" CBER, August 1996.
International Conference on Harmonization; Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin. Federal Register, Thursday, September 24, 1998.
International Conference on Harmonization; Q5D Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products. Federal Register, September 21, 1998.
International Conference on Harmonization; Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products. Federal Register, Wednesday, August 18, 1999.
International Conference on Harmonization; Guideline on Validation of Analytical Procedures: Definitions and Terminology. Federal Register, Wednesday, March 1, 1995.
International Conference on Harmonization; Guideline on the validation of analytical Procedures: Methodology. Federal Register, Monday, May 19, 1997.
Guidance for Industry Bioanalytical Method Validation, May 2001. FDA, CDER & CVM. (NOTE: this guidance is not applicable to CBER regulated products, but the concepts were generally considered)
SOP 9300R001 "DMPQ Review Responsibilities for the CMC Section of BLAs" effective date January 31, 2001.
SOPP 8410 "Determining When Pre-License/Pre-Approval Inspections are Necessary"

REVIEW

Tab "Summary of Changes" page 32. Serono notes that most of the changes have already been reported in amendments or updates to the annual IND reports. The changes below are for the drug substance.

Section 2.2.1, page 35. The facility changes at the bulk drug manufacturer XXXXXXXXXX

Other changes were made to the supporting units outside the IFN Beta-1a dedicated facilities XXXXXXXXXX

ISSUE: "Guidance for Industry: For the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use" CBER, August, 1996 under II.B.4 states that contamination precautions states in part, "…air quality classification of room or area in which operation is performed…" No information on the non-viable particulate classification of the area is provided. However, the issue is very minor as the only room that would be required to be classified is XXXXXXXXXX, and it is highly unlikely that

the classification of the room would not be consistent with other purification rooms. *See telecon with Serono, which is described below.*

Serono states that additional changes occurred in 2000 XXXXXXXXXX. An updated list of contract testing laboratories are listed in table 2.2.2.1-1 on page 37.

The SOP for sampling and testing new working cell banks for use in the future is provided (section 2.2.2.1). (NOTE: Establishment of a new working cell bank from a previously approved cell bank are allowed to be reported as annual reports in the CBER "Guidance for Industry Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biologic Products")

Serono is also providing for the supply of XXXXXXXXXX.

XXXXXXXXXX.

Serono has changed its policy for the preparation and acceptance of new production reference standards (section 2.2.7). Serono is proposing to change the specifications and test methods for release and testing of bulk purified IFN beta-1a (sections 2.2.8.2).

Serono has submitted updated stability data to support XXXXXXXXXX.

The changes for the drug product, manufactured at XXXXXXXXXX are described below.

The XXXXXXXXXX facility has undergone some changes –XXXXXXXXXX (section 2.3.1). Two new FDA licensed suppliers of albumin (XXXXXXXXXX) have been added (2.3.2). Lastly, the packaging of the Rebif pre-filled syringes has been modified to include a rigid needle shield protector to minimize inadvertent damage to the needle (section 2.3.3).

Section 2.2.2.1 page 61. This is a listing of the working cell bank acceptance criteria. In general, the test and acceptance criteria appear to be in accord with CBER's "Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals (1987)." However, there are some specific tests not conducted, e.g., XXXXXXXXXX. NOTE: Review responsibility for this section is by the product office (DMPQ SOP 9300R001, 1/31/2001).

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ISSUE: Based on the observation from the pre-approval inspection regarding mycoplasma contamination, and the possibility of the contamination originating from XXXXXXXXXX, the validation (for lack of mycoplasma) of XXXXXXXXXX should be discussed with the firm. *See telecon with Serono that is described below.*

Section 2.2.2.2.2 page 68. As noted previously, Serono will change from a XXXXXXXXXX.

Section 2.2.2.2.3 page 71. Serono is proposing to provide for an alternate supplier of XXXXXXXXXX.

Section 2.2.2.3 page 72. This section describes a minor change in the cell culture process. The change is in the acceptable range of cells seeded. Currently, the range is XXXXXXXXXX cells per tissue culture flask. The proposed change is to make the specification XXXXXXXXXX cells per tissue culture flask

Section 2.2.2.4 page 73. This section describes the modification to the in-process cell culture control parameter, i.e., the amount of IFN beta-1a in the cell culture harvest (the current specification was described in Volume 3, page 342 of the initial BLA). The current specification is greater than or equal to XXXXXXXXXX, and the proposed specification is greater than or equal to XXXXXXXXXX.

Section 2.2.2.4.1 page 75. This section describes the rationale and data to support removing the XXXXXXXXXX.

XXXXXXXXXX.

Section 2.2.3 page 80. Serono proposes to be allowed to XXXXXXXXXX.

Section 2.2.5.1-1 page 86 – 95. A flow diagram of the IFN beta-1a manufacturing process is presented.

Section 2.2.5.3 page 102. Serono is deleting some in process tests performed during the XXXXXXXXXX.

Section 2.2.6 page 107. Bulk drug shipping validation studies are described. The new shipping container has been shown to maintain the XXXXXXXXXX temperature for XXXXXXXXXX hours instead of the previous XXXXXXXXXX. Shipping validation was conducted at XXXXXXXXXX as well as monitoring of temperature during actual shipment. The temperature data was recorded every XXXXXXXXXX during the validation studies. The results are presented in three tables, (one table per package validation) 2.2.6-1, 2, and 3. The data presented confirm that the with the specified amount of XXXXXXXXXX, temperature can be maintained below XXXXXXXXXX. Tables 2.2.6.2-1, 2, 3, and 4 confirm that temperature specifications are met during actual shipping.

Section 2.2.6.2 page 111. The results of an 3 actual shipments of bulk product between the XXXXXXXXXX sites, than with shipment of the container (without product) back to XXXXXXXXXX to simulate worst case conditions. The data show that the temperature and amount of XXXXXXXXXX meet specifications.

Section 2.2.7.1 page 113. Serono is proposing to replace some of their XXXXXXXXXX.

Section 2.2.8.1 page 122. This section contains the validation data for the XXXXXXXXXX.

Section 2.2.8.1.2 page 132. This section contains the validation data to support the removal of the XXXXXXXXXX.

Section 2.2.8.1.3 page 135. The section contains the validation data to support the removal of the XXXXXXXXXX test. The removal of XXXXXXXXXX is in accord with recommendations in the ICH "Note for Guidance on impurities: Residual solvents" in that XXXXXXXXXX is not considered a solvent. XXXXXXXXXX. The data accumulated show that levels of XXXXXXXXXX are consistently less than XXXXXXXXXX in the final bulk IFN beta-1a. The removal of this specification appears well justified.

Section 2.2.8.1.4 page 138. This section provides data with regard to the change in the XXXXXXXXXX test. The change in the test is to make the test a limit test instead of a quantitative test. The results of the testing on production lots since the beginning of manufacture show that the results are consistently below the limits of quantitation of the test. The specification of no more than XXXXXXXXXX weight/volume remains unchanged.

Section 2.2.8.1.5 page 140. This section provides data to justify removal of the test for XXXXXXXXXX.

Section 2.2.8.2 page 143. The validation methods for the XXXXXXXXXX and modified XXXXXXXXXX test are presented in this section with the results. The methods are validated in accord with the ICH guideline, "Validation of Analytical Methods: Methodology." Specifically, the XXXXXXXXXX method is validated with regard to precision, accuracy, specificity, linearity and range, and robustness. The validation data presented on pages 157 through 161 support the conclusion that the XXXXXXXXXX method is precise, accurate, specific, linear, and robust.

Section 2.2.8.2.2 page 162. The validation methods for the modified XXXXXXXXXX test are presented in this section with the results. The test used for determining XXXXXXXXXX limits is a XXXXXXXXXX. The modification of the test is the replacement of the XXXXXXXXXX. For this validation, Serono used ICH guidance "Validation of Analytical Methods: Definitions and Terminology." Precision, quantitation limit, specificity, and robustness were assessed. The data presented from page 163 through page 168 support the conclusion that the method can be modified and remain precise, specific, robust and provide good assurance that the XXXXXXXXXX amounts remain within specifications.

Section 2.2.8.3 page 168. The validation methods and results for the elimination of the XXXXXXXXXX residue test are presented in this section. XXXXXXXXX.

Section 2.2.9 page 173. Updated stability data for the bulk stored at XXXXXXXXX at the XXXXXXXXX. Stability data for up to XXXXXXXXX are presented for XXXXXXXXX batches (lots XXXXXXXXX) and XXXXXXXXX batches (lots XXXXXXXXX). The stability testing protocol with results is presented in table 2.2.9-1 on page 174 through page 181. All specifications were met.

Appendix 1, page 185. The CoA for XXXXXXXXX, supplied by XXXXXXXXX, is provided.

Appendix 2, page 187. The CoA for XXXXXXXXX is provided.

Appendix 3, page 197. a reference article describing the typical concentration range of XXXXXXXXX in pharmaceuticals. Page 201 – articles on characterization of protein glycosylation by XXXXXXXXX.

Attachment 1 – page 228. This section provides background and validation data with regard to a XXXXXXXXX in the purification process for bulk interferon beta-1a. The in-process control specifications (and final specifications) remain unchanged. Comparison of the current process and the XXXXXXXXX process are delineated on page 236.

Section II.A page 239. Under section A.2. Serono describes the batches characterized in their validation studies. One bulk batch, XXXXXXXXX manufactured from the XXXXXXXXX process was extensively characterized. The current scale reference standard, XXXXXXXXX was also characterized by the same tests. The XXXXXXXXX validation batches were XXXXXXXXX.

ISSUE: Was there a XXXXXXXXX batch, and if so, what happened to it? How many batches were initiated, and did any fail? *See telecon with Serono which describes the lot numbering system.*

Page 241 provides the SDS page results for XXXXXXXXX, as well as buffer controls and low molecular weight markers. XXXXXXXXX focusing was performed on XXXXXXXXX with the results shown on page 243 (with controls). Page 245 presents a XXXXXXXXX profile of XXXXXXXXX and XXXXXXXXX with highly similar results. XXXXXXXXX mapping and XXXXXXXXX analyses were conducted on XXXXXXXXX – the procedure is described in detail in attachments 2 & 3 respectively.

Section II.B page 293. Table C.2-1 presents a flow diagram (in a tabular format) of the interferon Beta-1a process, with changes between the current and XXXXXXXXX noted. The tests to be modified or deleted were noted previously in this review memorandum. The process remains the same, however, bulk substances can be

transported at various points in the process to the XXXXXXXXXX area of the plant. The XXXXXXXXXX area is not licensed, but is used for interferon manufacture for non U.S. markets. Material that is transported to this area is not used in product that will be marketed in the U.S.

Section C.3.c.1 page 304. This section describes the changes to the bulk. A flow diagram on page delineates the size and number of XXXXXXXXXX up to the XXXXXXXXXX bulk stage.

Section C3.c.2 page 306. The purification process is described, with a number of tables describing and delineating the changes in the purification processes on pages 307 to 312.

Section C.3.c.3 page 326. A listing of the current XXXXXXXXXX in-process control is presented in table C.3.c-2. As noted, the changes consist of deletion of XXXXXXXXXX.

Section II.D page 332. A description of the process validation studies for the XXXXXXXXXX process is described here. XXXXXXXXXX.

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Section D2.b.1.2.1 page 334. The step yields, overall yield, and batch size during the XXXXXXXXXX process at each step in the purification for 5 XXXXXXXXXX up batches. Numerous tables presenting data from the purification step show that the in-process specifications are met.

Section D.2.c.2.4 page 354. Table D.2.c.-7 provides the endotoxin results for five XXXXXXXXXX batches and for 2 batches of the current scale. Endotoxin results at the XXXXXXXXXX, and bulk stage are shown – all results at all stages are at the limit of detection for the XXXXXXXXXX assay. Table D.2.c.2.5 provides the results for the same batches for the XXXXXXXXXX assay.

Section D.2.c.3, page 356. The XXXXXXXXXX step was reassessed for viral clearance as the XXXXXXXXXX. The same model viruses were used for the XXXXXXXXXX as were used for the current scale viral clearance validation. The results are presented in table D.2.c-9 on page 356. The results appear comparable, with an approximate XXXXXXXXXX decrease at the XXXXXXXXXX in viral clearance for XXXXXXXXX.

Section F.1.a.1 page 358. The specifications for the bulk drug substance at the XXXXXXXXXX process are listed – the specifications remain the same as for the current scale bulk drug substance.

Section II.H page 366. The drug substance stability testing protocol and results are presented in this section. The batches tested were XXXXXXXXXX. Results for the XXXXXXXXXX bulk drug substance at XXXXXXXXXX for up to XXXXXXXXXX, and results at XXXXXXXXXX for up to XXXXXXXXXX are shown. Table H.3.a-1 lists the tests that comprise the long-term stability testing regime. All results presented meet specifications.

Attachment 2, page 386. The XXXXXXXXXX mapping study for the structural analysis of interferon is provided in this attachment. The study was conducted at XXXXXXXXXX. Serono states that the site has been inspected by FDA and is certified by XXXXXXXXXX authorities to comply with cGMP.

Attachment 3, page 440. The final for the XXXXXXXXXX study for the structural analysis of interferon is provided here. Again, the study is conducted in accord with the EEC principals of good laboratory practice.

MEMO OF TELECON
DATE: 10/2/2001 FROM 9:25 TO 9:35 AM
TO: Pamela Williamson Joyce, Serono representative
FROM: Daniel Kearns, HFM-675
SUBJECT: Questions regarding May 16, 2001 amendment

I (DK) called and spoke to Ms. Williamson about Serono's amendment (dated 5/16/01) to their application for Rebif®. XXXXXXXXXX.

I said that I had the following points that I would like to have some further background on – I stated that we could discuss it in a telecon and that the information would not necessarily have to be submitted in writing – I would make that determination at the telecon.

1. I wanted to be advised if there had been any instances of mycoplasma contamination since the last inspection, and how the additional testing measures implemented by Serono were going.
2. I stated that no information (as required by CBER's CMC guidance) with regard to the non-viable airborne particulate classification was submitted for room XXXXXXXXXX (or if it was, I didn't see it). I said I would like some background on that room as far as classification, environmental monitoring, and validation.
3. I wanted some information on what testing and validation had occurred with the XXXXXXXXXX obtained from XXXXXXXXXX was done, as it was thought likely by Serono that the previous mycoplasma contamination problem originated from XXXXXXXXXX.
4. I said that I noted that in the sequence of validation lots, there was no XXXXXXXXXX. I wanted to know if there had been a lot XXXXXXXXXX or if something had happened to it. I also asked for all lots initiated specifically to support this amendment and their outcome (pass all specification, fail, under

review). I said if any lots had failed, the reason for the failure should be described.

The conversation concluded.
Prepared by D. Kearns on 10/2/01 at about 10:10 am.

On Wednesday, October 10, 2001, Mr. Richard Scotland of Serono returned my (DK) earlier call on the status of the call made to Ms. Williamson on 10/2/2001. Mr.Scotland had the answers to the questions I had previously posed. Below are the answers:

1. Mr. Scotland stated that there have been no further instances of mycoplasma contamination since the event noted in the last pre-approval inspection conducted by myself. Mr. Scotland's response also detailed the mycoplasma testing procedures, which remain the same as the procedures implemented post inspection. No further mycoplasma contamination has been found.
2. Room XXXXXXXXXX was always classified as class XXXXXXXXXXX. The function of the room has changed. The room is monitored and qualified (and re-qualified annually), as are the other purification rooms.
3. The XXXXXXXXXX is qualified as per Serono's procedures, and includes a GMP audit and a requirement that vendors who supply XXXXXXXXXX use facilities for collection and processing that are USDA approved.
4. The lot numbering system was changed –XXXXXXXXXX.